

Neural mechanisms of cognitive generalization across species: From hippocampus to cortex

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How do brains take what they have learned and apply it to new situations? This fundamental question sits at the core of cognitive generalization—a crucial ability that allows organisms to adapt to novel circumstances by drawing on prior experiences. While this mental flexibility enhances survival across species, the underlying neural mechanisms connecting different brain regions in rodents, primates, and humans remain poorly understood. Our review maps these neural pathways of generalization from hippocampus to cortex across the evolutionary spectrum. We show how hippocampal remapping and replay processes create abstract rules during generalization, with different hippocampal subregions handling distinct memory types. The prefrontal cortex emerges as essential for rule-based categorization across all species studied, while the orbitofrontal cortex drives value-based decision-making, and the posterior parietal cortex guides generalization through perceptual processing of past experiences. We explore the neural circuitry connecting these regions and examine how similar these brain structures and their associated behaviors are across species. Additionally, we discuss how disruptions to cognitive generalization manifest in various neurological conditions and their corresponding brain regions. This comprehensive analysis not only clarifies the neural foundations of cognitive generalization but also suggests promising directions for interventions targeting related neurological disorders.

Brain Medicine July 2025;1(4):37–49; doi: <https://doi.org/10.61373/bm025w.0047>

Keywords: Adaptive behavior, cognitive generalization, comparative neuroscience, cross-species cognition, hippocampal function, memory generalization, neural circuits, neurological disorders, prefrontal cortex function, rule learning

Introduction

Experience is the best teacher of life. The ability of fast adapting from past experiences to novel circumstances is required for survival and better living in animals and humans. Generalization is the presentation of adaptive performance which requires the abstraction of common rules or concept or pattern features from learned tasks of specific behaviors and then that be transferred and applied to similar but novel circumstances. The process of generalization can be basically divided into three steps: firstly, individual experience of an event, situation or a task is obtained; secondly, the event, situation or task should be abstracted as a concept or a rule; thirdly, the abstracted concept or rule is employed into subsequent similar events or tasks. Taking a simple example, once a man has learned a skill from a specific sport game badminton, he could quickly get the skills of how to play a similar sport game tennis. During this process, the memory information of playing badminton has been abstracted as a common feature or rule that can be generalized to the learning process of playing tennis. Generalization enables the identification of commonalities and relationships among diverse events, objects, and actions via semantic learning, concept learning, category abstraction, structure learning, and etc., thus being applicable in diverse high intelligent behaviors, such as, perception, learning and decision-making, and future planning (1).

Identification of common features or rules is the most prominent step for generalization. This is based on the comparison and interactions among memories from different tasks, which is also supported by the geometry of abstraction (2). Abstract rule is different from concrete rules; concrete rule is based on simple spatiotemporal links between objects, events, and actions, while abstract rules are complicated, applied to multiple circumstances, and generalized from past to novel circumstances (1, 2). For a particular abstract rule, the core of the rule is rigid and does not change with environmental factors.

Transfer is another key step of generalization that the abstracted rules or structural knowledge between elements are transferred rather than knowledge of the individual elements themselves. This is thought to be critically dependent on the instability of memory, which is helpful for transferring (3). Transfer of structural knowledge in spatial and nonspatial tasks both can improve efficiency. Memories, or the neurons that carry them, show variability in response to changes in the environment under the guidance of abstract rules. This shows the mutual unity of the transferred structure and the abstract structure in representing generalized behavior. One situation can be abstracted into a structure, which maps to a new and similar situation with different sensory input. The solution is inferred with a shorten process. This phenomenon can be explained by psychology as “the formation of learning sets” (4).

According to these two important properties of generalization, there are two types of neural populations with opposite characteristics that cooperate to support generalization. A single neuron showing stable firing pattern or neural ensembles converging onto a low-dimensional feature for representing the common structure that supports generalized cognitive operation. On the other hand, there also exists neurons with flexible property, which would change their activity pattern to cope with variable external factors. This change is directional, not random, which is followed by the main process for characterizing common features of tasks.

Regarding the limited study of generalization but its importance for adaption and survival, in this review, we focus on reviewing the neural mechanism of generalization of spatial and nonspatial representations in different cortical and subcortical brain regions, including hippocampus, prefrontal cortex (PFC), orbitofrontal cortex (OFC), and posterior parietal cortex (PPC) from rodents to primates and humans, which will explicit a brief frame for the neural manipulation of generalization from hippocampus to cortex and provide cues for revealing the circuitry connections among these brain regions in modulation of the cognitive generalization.

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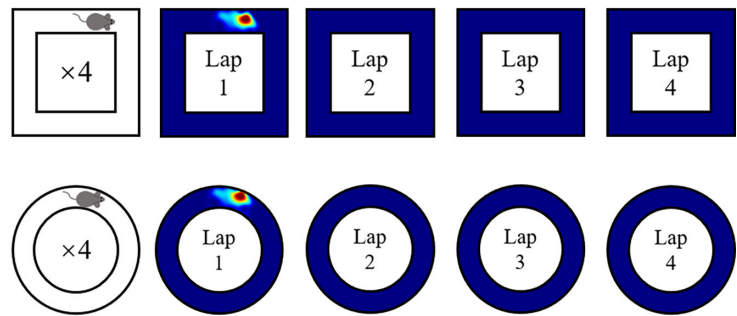
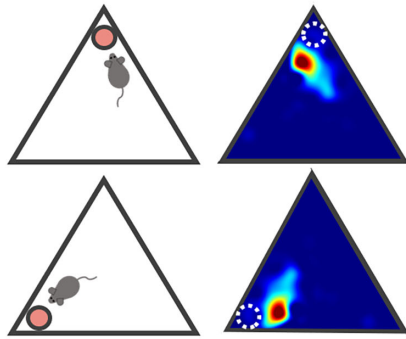
Received: 18 December 2024. Revised: 5 March 2025 and 19 March 2025. Accepted: 25 April 2025.

Published online: 20 May 2025.

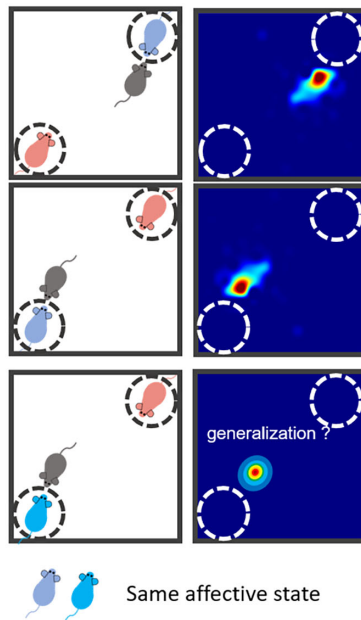




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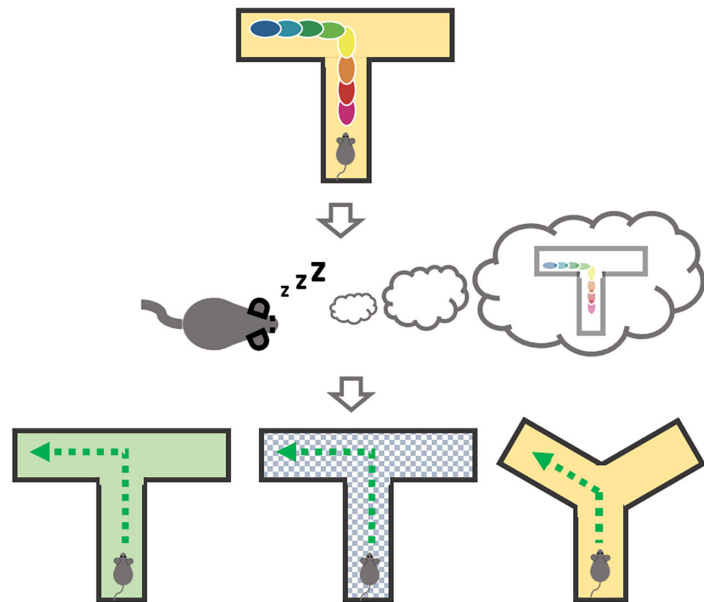


Figure 1. Hippocampal remapping and replay in cognitive generalization. (A) Left: Hippocampal neurons show remapping activities to represent the altered spatial stimulus; Right: In this article (70), the event-specific rate remapping neurons support transfer learning on two geometrically distinct mazes, from square maze to circular maze. (B) In this article (60), hippocampal CA2 neurons show remapping activity to same mice with changed locations. While it needs to be further explored whether CA2 cells also remap to another mouse with same state compared with the previous one. C, Hippocampal neural replay guides mice to accomplish the similar tasks with different contexts. The replay activity occurs during sleep and awake state.

Hippocampal Replay and Remapping Underlie Generalization

Hippocampus encodes spatial information, which links sensory features to context. It is well established that hippocampus contains place cells which store memories of specific locations. Hippocampal place cells exhibit maximal firing especially when a specific spatial place field is occupied, which is not responding to simple sensory stimulus or specific motor behaviors (5, 6). Each place cell is considered to possess individual place fields and correspondingly each location is encoded by a particular cluster of place cells, thus leading to a comprehensive mapping of an environment in hippocampus (7). Hippocampus not only encodes spatial information, but also maps nonspatial dimension. It is shown that hippocampus supports general cognitive processes (8) and bilateral hippocampus support generalization of gradual internal learning (9). Hippocampus has been found to selectively fire or cease to fire when mouse perceives nests or beds, suggests that hippocampal neurons have the ability to extract fundamental features and commonalities from various episodic experiences and to then generalize them into abstract concepts and knowledge from behavioral experiences (10). Hippocampal neurons have also been reported to respond to visual (11), auditory (12), and olfactory cues (13, 14) or combinations of those. When hippocampus encodes both nonspatial

and spatial features of an experience, a complex and highly organized ensemble is introduced to build a schematic framework for multiple related memory elements (15). During mapping the environment through spatial and nonspatial information, the neurons in hippocampus that encode spatial and sensory representations show characteristics of replay and remapping, which may play crucial roles in generalization (Figure 1).

Hippocampal Replay During Sharp-wave Ripples Retrieves Experience to Future Decisions

Replay is the sequential reactivation of hippocampal place cells that represent previously experienced behavioral trajectories, which is considered as a crucial characteristic of hippocampus processing, storing, and updating of event memories. Early in 1989, Pavlides and Winson firstly reported the replay phenomenon and observed that place cells elicit higher firing rates and increased bursting during non-rapid eye movement and rapid eye movement (REM) sleep, which is considered as an important form of memory processing (16). Later study found pairs of cells whose place fields overlapped during behavior tended to fire together during subsequent sleep, which is defined based on the presence of hippocampal sharp-wave ripples (SWRs) (17). The sequential firing patterns of



hippocampal place cells for cognitive representation in spatial navigation that encodes previously experienced behavioral trajectories can be replayed in a temporally time-compressed format of either forward or reverse sequence during non-REM sleep state and during awake state, especially in a transient halt period (16–18). Hippocampal circuit could also replay random trajectories of former cognitive map, which has potential to generate future behavioral outcome, especially generalization (19). It has supposed that generalization and structural learning may partially depends on hippocampal replay, which is crucial for extracting task rule from awake experience during replay initiation (20, 21).

It is widely accepted that sleep replay is linked to memory consolidation (17, 22). Learned memory reactivation during sleep could be integrated into former cognitive schema (23). Daytime naps facilitate generalization of concept learning both in infants and adults in human studies (24–26). Neural recording experiments suggest hippocampal replay during SWRs may act roles in past experience consolidation and future plan (27, 28). Especially, replay during sleep SWRs show potential to reorganize the spatial representations and iconic events of previous memory, which suggests that multiple experiences are integrated during sleep SWRs to support the form of generalization (29, 30). Through downsampling and compression, the hippocampal replay representation is effective in integrating knowledge, helping to generalize to a level similar to the exact veridical replay of experience that improves generalization performance. Therefore, it represents a feasible and efficient memory consolidation solution without compromising effectiveness (31). Feedback blockade of SWRs during a learning process prevents integration spatial path optimization, demonstrating the necessity of replay for generalization (32).

Awake replay during immobility might represent neuronal trajectories of either current environment or previously experienced environment and is associated with the processes with ongoing memory-guided preparatory behavior, such as foraging, exploratory, goal-directed or planning behaviors (18, 33, 34). Studies have suggested awake replay is important for memory-guided behavior and cognition (33, 34). Different from replay in sharp waves during SWS, replay in awake state occurs immediately after spatial experiences in a temporally reversed order, that allows immediate evaluation of the preceding events in precise temporal association with a current event, which maybe considered as an integral mechanism for learning from recent experiences (35). It is recently reported that awake replay is mainly dominated in past experiences of locations with a reliably delivered reward and those not recently been visited, suggesting the contribution of memory-related processes by awake replay is due to its role in memory storage rather than in directly guiding subsequent behaviors (36).

Awake SWRs occurred in hippocampal replay of past experiences, which are able to predict choice of correct trials than error trials in memory-guided decision-making (37). Hippocampal replay in awake state contributes to decision-making especially during spatial navigation (37, 38). Awake SWRs are suggested to support rearrangement of stored information with novel combinations, in order to reactivate new firing pattern for future decision-making. The replay in SWRs can preferentially occurs in rarely experienced trajectories, to maintain integrity of cognitive map or as a prereplay for prospective events (39). While the contrary finding indicates that hippocampal replay shows specific past experiences, not a plan of future choice (36). And it is reported that there were no trial-by-trial relationships between replay content and subsequent behavioral trajectory (32, 40), suggesting that replay would not affect subsequent behavior. The controversial conclusion may be caused by different memory types of tasks. Trajectory replay of hippocampal CA1 in reference memory tasks is proposed to predict future decision goals. On the contrary, the trajectory replay in working memory only exhibits previous goal arms (41). Nevertheless, replay could still facilitate the long-term consolidation, integration, and maintenance of particular experiences as a storage role, preparing for future tasks served in generalization.

Moreover, in human study with functional MRI (fMRI), hippocampal replay reflects the order of previous task-state sequences, building representations of complex and abstract tasks (42). And replay in human hippocampus prefers weakly learned information and predicts subse-

quent memory performance (38). Through magnetoencephalography to measure fast spontaneous sequences of representations, Liu *et.al.* proposed that an abstract replay is a mechanism for generalizing structural knowledge to new experiences. Through replay, not only are the experienced subtrajectories connected, but also the sequence in the new order by abstract structural knowledge can be rebuilt (21). Recent researches have shown that SWRs in hippocampus act as potential functional biomarkers of memory impairment in neurodegenerative diseases, especially in Alzheimer's disease (AD) (43–46). It is reasonable to assume that the replay ability might be decreased in AD mice that could not be applied to represent replay information to guide subsequent tasks for generalization.

Hippocampal Subregional Remapping in Spatial and Nonspatial Aspects Adapts to New Environment

In reality, it is comprised of multiple modalities of sensory features that special spatial information is encoded by each modality for navigation, thus leading a combination of sensory and abstract reference frames in brain maps (47). Under multisensory environments, hippocampal place cells can reorganize their population representations in response to the changing factors of environmental geometric (48) or nongeometric cues (odor, color, and etc.) (47, 49), the process of which is well known as “place field remapping” or simply “remapping” (50). Remapping often occurs by changes of sensory inputs (51), motivational state (52), and other inputs from outside environments. Intensive studies have classified remapping into several types, including “global remapping,” “null remapping,” “partial remapping,” “rate remapping,” and even “graded remapping” in an attempt to distinguish different mnemonic conditions (7, 53–55). The remapping of hippocampal cognitive map driven by experience encodes location through spatial and nonspatial dimensions to predict and estimate new environment (56). The working pattern of hippocampal remapping makes it with great potential to abstract events into putative concepts or rules, promoting transfer learning.

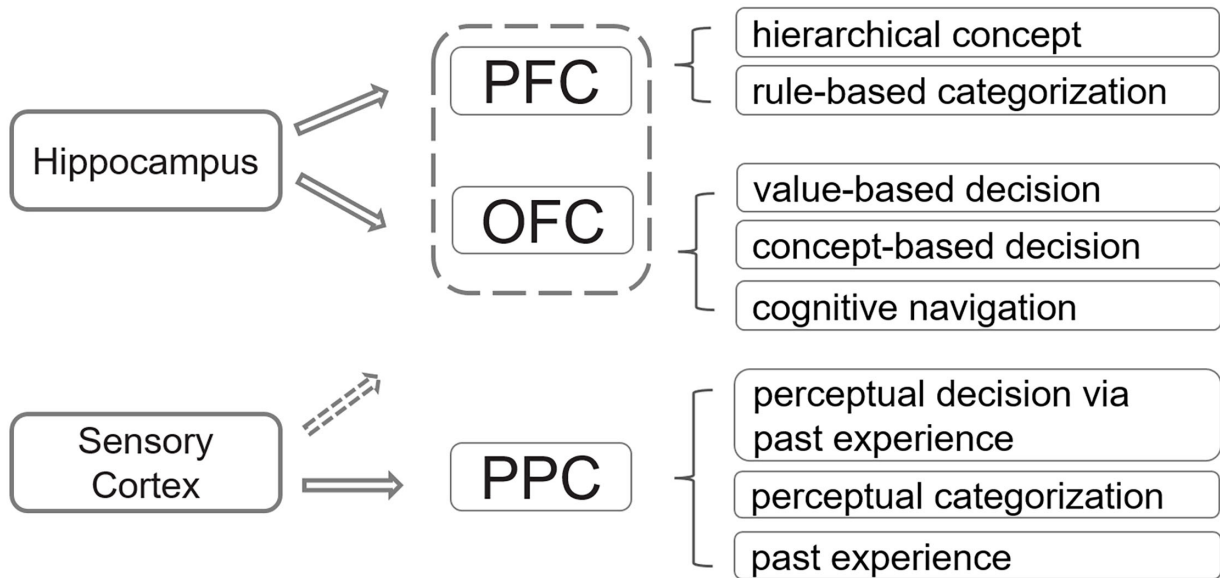
Numerous studies have reported all the hippocampal subregions, including CA1, CA2, CA3 and dentate gyrus, possess place cells that encode place fields in navigation. When encoding experiences in new environments, hippocampal neurons show heterogeneity that CA1 place cells fire faster than CA3, while CA1 place cells gradually shift backward with experience and remap when under re-expose to the environment one day later. Oppositely, CA3 place cells fire gradually but display less backward and more reliable trial-to-trial and day to day dynamics (57). CA3/DG remapping show stronger episodic associative information, which reflects the sight effects of episodic learning (58). CA2 place cells exhibit different activity patterns from those of CA1 and CA3 that their firing rates change over time even in the same environment and do not persistently code for space or contexts (59). CA2 neurons remap to social stimulus, termed social-remapping cells, indicating the preferential reactivation of CA2 neurons encodes social representations following social experience and may act a role in social memory generalization (60). It is interesting but unknown whether CA2 neurons have potential in remapping to abstract emotional states for reorganizing social subjects (61, 62).

Under different circumstances, hippocampal firing has been verified to contain both stable encoding (63) and transient programming (64). For hippocampus and its related circuits, upstream brain regions (like CA1-projecting CA3 neuronal ensembles or CA1-projecting MEC neuronal ensembles) tend to show reproducible firing patterns and structural representations, which lead downstream CA1 neurons remapping in a directional manner to support the generalization of transitive structure (65, 66). This indicates that remapping of hippocampal place cells is thought to play a crucial role in learning generalization. Therefore, this combined stability and flexibility leads hippocampal circuits to encode both external fixed circumstance and draw cognitive maps with change environment of related experiences. Firing fields of hippocampus could be generalized with progress through behavior, which could be useful for linking events in episodic memory and for planning future actions (67).

Hippocampal CA1 neurons exhibited nonspatial event-specific elevated firing activities by transient theta sequence, which can be flexibly



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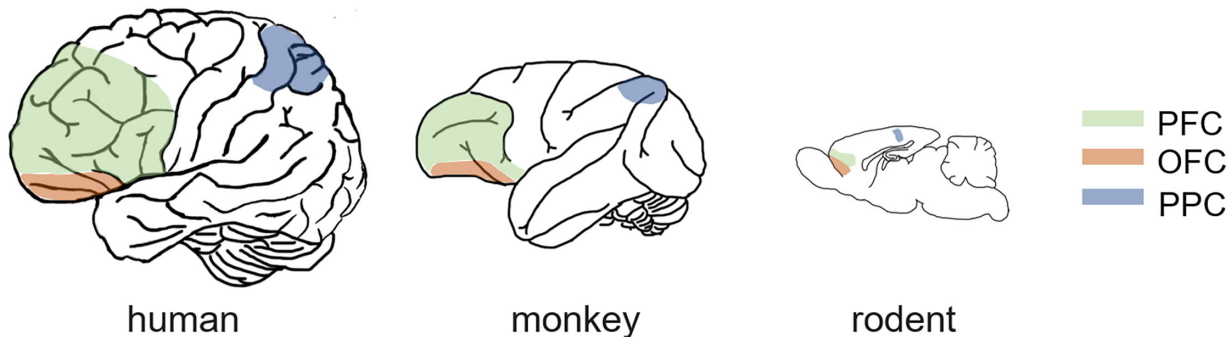


Figure 2. Neural circuits associated with three cortical regions in cognitive generalization with different manifestations from different species. (A) Emotion-related brain regions mainly project to PFC and OFC; Sensory-related brain regions mainly project to PPC. (B) PFC, OFC, and PPC show similar brain area distributions from humans, monkeys to rodents.

reorganized (68). Through a tilted and rotated rectangular track experiment, CA1 place cells are shown to be sensitive to three-dimensional orientations that a majority of place cells change their place fields unpredictably, leading a partial remapping; while a minority kept the same field in x-y coordinates of the track, neglecting z-axis. Reorganization and reactivation of hippocampal assemblies with SWRs represent the formation and expression of new spatial memory traces, suggesting the generalization potential (69). Sun *et al.* found a specific kind of neurons in hippocampal CA1 that encode generalized information from a designed task instead of precise sensory information. The neurons, called event-specific rate remapping cells, show lap-specific activity in a square maze composed of four indistinguishable lap events with a reward only on lap 1. This kind of activity can transfer from square maze to rectangle, circular and even nonspatial factor changed maze, which suggests the hippocampal CA1 activity pattern not only reflect events but also generalize these events as rule experiences (70). A certain population of hippocampal CA1 place cells has also been reported to present environment orientation and topology. The orientation selectivity is contributed by a redistribution of place cells remapping, which indicates that the prior experience generalization improves predictability of future environmental representations (71).

Hippocampal neurons in primate study encode position within an abstract value space and construct a map for an abstract cognitive variable through place like representations (72). In human study through fMRI, hippocampal remapping and entorhinal grid realignment predict spatial representation, which show ability to distinguish among different

navigational experiences (73). Hippocampus is also involved in reasoning over social hierarchies (74). Whittington *et al.* proposed the Tolman-Eichenbaum Machine (TEM), which introduces that hippocampal place cells remapping between environments represent generalization (66). The TEM is capable of learning the abstract set of relationships that govern social hierarchies (66). Furthermore, fMRI studies in humans have shown that hippocampus can encode more cognitive variables, such as the sequential nature of a nonspatial tasks (42) and social interactions (75, 76). The human studies integrated with rodent and primate researches together to reveal the crucial role of hippocampal remapping in spatial and nonspatial related memory generalization.

The Prefrontal Cortex Required for Abstraction and Categorization is Essential for Generalization

Generalization requires the abstraction of pattern features or principles that are commonly occurred across experiences, which is in certain degree dependent on the ability of PFC neurons (3, 77). Initially, it was considered that the PFC supports abstract, or verbally-mediated, semantic knowledge rather than sensory-based properties (78). While, it is now widely accepted that PFC neurons are capable of encoding a diversity of information by stimulation of different sensory modalities and controlling "high order" behaviors, which include category abstraction, rule learning, etc. (79–82). Regarding to category abstraction, it can be divided into the specific and generalized representations that are organized and determined by different subregions of PFC (83) (Figure 2). In a dot-pattern categorization task performed by monkeys, the ventral PFC is shown to be



responsible for processing more low-level abstractions via bottom up dynamics of stimulus-locked gamma power and spiking, while the dorsal PFC (dLPFC) is capable of processing more high-level abstractions via top-down dynamics of beta power and beta spike-local field potential (LFP) coherence (84). In humans under a reinforcement learning paradigm, it was demonstrated the rostrocaudal architecture of the frontal cortex is responsible for rapid rule learning at multiple levels of abstraction, especially under novel behavioral context (85), indicating its capacity of generalizing past learning to new problems. Patients with PFC lesions exhibited impaired acquisition of second-order in abstract rule learning when performing a hierarchical reinforcement learning task (86). In monkeys performing a rapidly learned task based on the formation of abstract concept, bilateral lesion of lateral PFC significantly impairs rule reversal rather than acquiring roles, while would not affect either rule tasks without concept-based role. These implicate that lateral prefrontal cortex (LPFC) is responsible for modifying abstract rule after establishment, which might not be renewed in the absence of PFC (87). Considering the importance of PFC in categorization and abstraction, we will illustrate the role of PFC in generalization in terms of both individual neural activity and neural ensembles representation.

In rodent experiments, mice learn rule-based categorization and generalize to novel stimuli during the entire learning process. During learning, neurons in the PFC display different dynamics in obtaining category selectivity and different engagement in subsequent rule-switching tasks, which is the key to rule-based categorization (88, 89). When rats perform a medial prefrontal cortex (mPFC)-dependent rule-switching task on a plus maze, the principal neuron in mPFC primarily represent a generalized form of space via encoding the relative position between the start and the goal. And independent of hippocampus, mPFC can imitate entire spatial trajectories via replaying ordered activity patterns in generalized positions, indicating its role in flexible behavior (90). In mouse, through repeatedly imaging individual cells in mPFC during a "Go"/"No Go" rule-based categorization learning paradigm, Reinert *et al.* reported that a subpopulation of neurons is selectively and uniquely responsible for categories and reflect generalization behavior. Therefore, the categorical neuronal representation is acquired gradually rather than temporarily recruited, indicating that neurons in the mPFC are part of the specific semantic memory of the learning category (91). Neuron ensembles in mPFC of rats are responsible for applying abstract structure to a new situation based on their selective firing patterns, which become less selective for perceptual features but more selective for common rational features and immediately generalize to the new situation (92), suggesting mPFC has the ability of developing a knowledge structure and adapting it to new experiences.

In monkeys performing "match/nonmatch rule" experiment, which requires rule-based comparisons of similarities or differences between stimuli that generalize to multiple examples, single neuron recording demonstrates that some prevalent neuronal activity observed in both dorsolateral PFC and ventrolateral PFC reflects the coding of abstract rules (93, 94). When performing visual symbol response in a repeat-stay strategy, neurons in mPFC of monkeys display selective activity in choosing which is not only based on fixed mapping, but also based on abstract strategies during trial-and-error learning (95). In a series of studies of number rules, a high proportion of recorded cells in the PFC encodes information about the number, generalized across changes in the physical appearance changes (96, 97). In rule switching tasks, monkeys are capable of switching between rules and generalizing the rules to new examples. The substantial proportions of neurons in mPFC show constantly changing neural activity to adapt switching rules (98, 99). In monkeys performing a cognitive-set-shifting task, a cluster of neurons in the inferior arcuate region of PFC were identified to be selective for shifting cognitive set. While, pharmacological inactivation impairs the performance of behavioral shifting, further suggesting this region supports cognitive shifting between rules (100). The dorsal anterior cingulate cortex and putamen of monkeys exhibit different representations during new rule learning that neurons in the cingulate cortex mainly rotate toward the role for a policy searching while neurons in the putamen exhibit a magnitude increase following the rotation of cortical neurons for enhancing the con-

fidence of the newly acquired role-based policy (101). Neurons could rotate to decrease the angle to rule in order to change strategy of learning. For single neural activity, the readout of a neural ensemble can improve performance because of a change in individual neuron properties or because of a change in weights given to each neuron by a readout node.

Neural populations in response to structure in PFC show representative features of generalization in the neural geometry level that are not apparent at the level of individual neurons. Through a linear classifier to decode a large number of different variables, when monkeys perform serial-reversal learning tasks with different hidden and explicit variables, it was observed that neural ensembles in PFC represent multiple variables in a geometry to reflect abstraction and support generalization in novel situations (2). The mPFC stores representations of the common spatial structure, termed schema, across environments. While, through high-resolution fMRI approach determining the roles of PFC and hippocampus in human participants during spatial environments retrieval, pattern separation and repulsion have been found in different subregions of hippocampus (102). Similar to hippocampus, neural activities in mPFC holds similar firing patterns between places with similar task contexts. What's more, the mPFC replays organized sequences of positions indicating generalized behavioral trajectories. The mPFC trajectory replay performs both in the forward and the reverse sequences, indicating that it is not a mere rehearsal but an abstraction of the original experience. Through regulation of hippocampal activity, neural representation of a subset of PFC ensembles generalizes across different paths, which provides a potential mechanism for generalization across individual experiences (103).

Memory processing through mPFC has been involved using prior experience to improve learning of new tasks (104). Activity in PFC is associated with representing the structure of ongoing tasks (105). Neural computational model of PFC underlies the framework of hierarchical predictive coding, which indicates individual neurons in mPFC encode multiple task variables with a more abstract stimulus value code. fMRI experiments in human study reported that the ventral medial PFC (vmPFC) and its functional connection with visual cortex, as top-down control of sensory cortices, construct abstract representations through a goal-dependent valuation process (106). Through novel tree-like categorization task performed by human participants and analyzed via computational model comparisons, it is shown that mPFC traces accumulated hierarchical conceptual knowledge along time, and mPFC and hippocampus both update trial-to-trail information, indicating mPFC and hippocampus are required for the integration of accumulated evidence and instantaneous updates into hierarchical concept representations as time goes by (107). In a compositional representation task, fMRI and multivariate pattern analysis demonstrated that LPFC can transfer practiced rule presentations into novel contexts, guiding cognitive performance in novel circumstances (108).

The OFC with Value-guided Characteristic Reestablishes Cognitive Map with New Information

The role of OFC in generalization depends on its pivotal function in decision-making, which is associated with the heterogeneity of OFC neurons. OFC shows different responses to sensory inputs during decision-making, such as relative and economic values (109, 110), reward- and value-based behaviors (109, 111–115), expected or predicted outcomes (116, 117), confidence estimates (118), cognitive map of task space (119, 120), regret (121), and credit assignment (122). Wilson *et al.* proposed a theory that OFC may encode the current abstract state of a task for reinforcement learning. They hypothesized that OFC can distinguish tasks with similar sensory inputs but different kernels, indicating that OFC can categorize events, based on different concepts (120). OFC encodes task structure representation as a more general role, which can also include value representation derived from the task structure.

Single neuron responses are essential for understanding representation in nature, for individual neuron contributes in a different way to the ensemble encoding of stimuli and performs a different profile of tuning a subset of the stimuli to provide high capacity and generalization. OFC



neural activity correlates with economic value, representations are usually much more specific to elements of task structure, indicating that OFC contains an abstract representation of decision confidence (123). OFC does not show specific activity in simple or even some complicated learning tasks. While, tasks that force animals to adjust their behaviors in light of new learning are generally dependent on OFC function. Outcome devaluation depends on OFC activity, which encodes specific sensory features of outcomes (111, 124, 125).

OFC has been reported to support abstract representation of multi-sensory decision-making (126). A statistical confidence computation and predicted behavioral reports of confidence can be underlined through OFC activity. Masset *et al.* found that single neuron in OFC of rats can generalize statistical decision confidence information regardless of sensory modalities to predict multiple confidence-guided behavior during decision-making (127). Researchers have found that OFC neurons respond transiently to the rule switching during reversal learning tasks. Through a reversal learning task for head-fixed mice, a subpopulation of OFC neurons was found to display remapping activity in order to respond to updated sensory inputs, and particularly, that dynamically interact with sensory cortex to implement computation and form plasticity for flexible sensory processing and adaptive decision-making (116). Zhou *et al.* reported that neural ensembles of OFC in rats can converge low-dimensional neural code across both problems and subjects to generalize common structure of the problems and its evolution, thus forming a schema for supporting a complex cognitive operation (128).

Primate studies show that OFC lesion significantly impairs the ability of acquiring and reversing the concept-based rule (87). OFC is essential to distinguish different concepts and classify similar rules. Through performing a Wisconsin Card Sorting Task by macaques, the neural firing rates in OFC change reliably for rule identity and rule category (129). The same group further found that the OFC neurons are also activated in relation to rule shifting during cognitive set reconfiguration (130). Social characteristics can also be encoded by OFC, which represents facial categories related to social and emotional behaviors. Neurons, called face cells, encode the intrinsic properties conveyed by the face and its expressions, suggesting that this cluster of neurons in OFC abstract social information through faces and generalize to other facial expressions with similar physical properties (131). Lesion studies suggest that the OFC involves the evaluation of decision outcomes and effectiveness of updating rules (132, 133).

In human studies with fMRI, OFC has also been proposed to act as a cognitive map of spatial task and provides strong support for the state representation theory of OFC (134). This experiment requires participants to conjecture the trial type, which is a hidden state that needs to be learned from previous trials. OFC is found to represent task states, rather than explicit values. Other human researches also proved that OFC represents hidden states (75, 135). OFC activity is also required for the distant and unseen future consequences of goal-directed actions (136). A theory model recently argues that representation of value in OFC is relevant to its more general role in representations of task structure (137). Together, neural recordings in rodents, primates, human imaging, and neural stimulation studies have highlighted the essential role of OFC in performing higher-order representations related to abstract information.

OFC is also involved in emotional processing. The dysfunction of the OFC may cause symptoms of affective disorders, such as anxiety, depression and impulsivity. It is reported that emotion-related diseases are also associated with cognitive dysfunction. Early life stress-mediated mice model shows impairment of rule-reversal learning, indicating deficit of generalization-related process might function as a potential indicator of OFC impairment-related diseases (138).

PPC with Perceptual Stimulus of Historical Experience Guides Generalization

PPC also contributes to generalization. This is not surprising since PPC plays an essential role in sensory-mediated decision-making and categorization behaviors that supports generalization to varying degrees. PPC contains two encoding patterns: heterogeneous encoding for specific representation and comprehensive encoding for globe representation, which

together shows potential advantage to generalization. For instance, neurons in the inferior parietal lobule in primates encode different types of movements, respectively, in a structured sequence (139), similar to rodents research in hippocampus, which represents lap numbers in round track (70). PPC has been shown to encode a large variety of sensory-, cognitive-, and motor-related signals during a wide range of behavioral contexts and tasks (140), including working memory (141, 142), spatial navigation (143, 144), especially in encoding for locations in egocentric space, decision-making (145), top-down and bottom-up attention (146, 147) and episodic memory (148). PPC seems to encode information in a low dimension, which can represent different aspects of physical feature, such as shape classification (149), movement direction, and counting number (150).

Recent findings indicated that the PPC plays an important role in memory updating (151). Using a goal-reaching task in mouse, it was shown that PPC implements and updates to forecasts, when prediction uncertainty decreases because of new sensory inputs (152). The PPC has been proposed to act as a sensory history buffer for use in a future relevant experience (153). PPC ensembles are required for both encoding and the recall of associated memory. Retrieval suppression of the corresponding PPC cell population dissociates experience from pre-exposed context and leave individual memories intact, which suggests that PPC ensembles can flexibly bind or unbind to different information. This process underlies that PPC abstract experience from events, leading to the formation of generalization. PPC is highly related to the processing of previous experience information, which represents previously learned sensorimotor associations to guide decision-making in seeking reward on new sensory stimuli. Inhibition of PPC decreases performance of reward based categorical decision-making on new sensory stimuli, which indicates that PPC is crucial for abstracting task rule from previous experience and applying that in similar tasks with new cues. PPC could encode previous category knowledge to counterbalance the uninformative influences.

It also suggests that PPC may act an important role in reward based generalization (154). For different task diagrams in working memory, PPC neurons carried far more information about the sensory stimuli of previous trials. Inactivation of PPC improves working memory performance and results in less interference with experienced stimuli (155). Although silencing PPC neural activities leads to opposite task performance in different task paradigms, this is consistent with the function of PPC in previous stimulus process, which is related to memory generalization. In addition, through long-term neural recording of PPC, the neural firing pattern of PPC has been found to be reorganized across days about task features. There exists a neural ensemble that represents a new activity pattern when mice learn a new associative task, indicating this neural ensemble possess malleable activity patterns that might be required for abstracting learned representations (156). The generalized categorical encoding in PPC suggests it is involved in a wide variety of abstract cognitive functions beyond categorization. PPC is most likely a node in the network mediating abstract cognitive computations.

Quite a few primate studies also show the function from categorization to generalization in PPC (also known as LIP in primates). In working memory based visual motion categorization task, categorization training influences cognitive encoding in PPC, suggesting task-specific mnemonic encoding in PPC. While PPC displays strong activity in both discrimination and categorization tasks. PPC is selectively engaged in cognitive abstraction (157). Parietal cortex is found to encode shape selective information of visual stimulus to present generic categorical outcomes. PPC neurons also form associations between different features. A same population of neurons can encode learned associations in separate task, which implicates a foundation of learning generalization (149). In number rule task, there is a substantial proportion of neurons in PPC cortex encoding numerical information, which is conveyed by auditory and visual stimuli, indicating PPC acting its role in multimodal representations of abstract numerical information (158–160). In addition, single neural activity in PPC can also represent rule shift in rule switching tasks.

In human study through fMRI, visual processing is divided between a ventral and dorsal stream specializing in object recognition and vision for



action. Dorsal stream has been reported to enhance action and identity information, leading to an abstract representation in PPC (161). PPC and primary motor cortex show a connection between motor memory formation and neural representation. This connection supports intrinsic (body based)-extrinsic (world based) space for generalization pattern, which indicates that representation of learning is based on a combination of local representations in intrinsic and extrinsic coordinates (162). PPC is more active during the execution of novel than that of practiced instructions but show similar activities between the execution phase and the instruction phase. This pattern implies that the PPC support cognitive processes in both the encoding and the execution of novel instructions (163).

Hippocampal-cortical Connections in Generalization

Cortex and hippocampus are strongly interacted by direct and indirect pathways. Many studies have highlighted interactions between the hippocampus and the PFC that acts an essential role in episodic memory. While we know little about the function of hippocampal-cortical interactions in generalization, there are three main pathways existing between the PFC and the hippocampus: Firstly, a monosynaptic projection is from ventral hippocampus to mPFC, as well as OFC. The complementary learning systems theory is proposed to discuss the generalization of hippocampus-dependent memories (164, 165). In this theory, the hippocampus represents individual memories, and the common features are abstracted by cortex. In the process of memory consolidation, the memory generalization emerges through information transformed from hippocampus to cortex. Secondly, the mPFC bidirectionally communicate with hippocampus through intermediate medium: thalamic nucleus reuniens (NRe). A model is reported to underlie the mechanism of the NRe's control of memory generalization (166), in which NRe regulates hippocampal excitability persistently, thereby controlling memory generalization (167). mPFC-NRe-hippocampus circuit may regulate memory generalization by actively controlling hippocampal remapping. Thirdly, the mPFC connects to medial and lateral entorhinal cortex, which produces strong projection to hippocampus. This pathway is required for processing object and event representations (168, 169). Hippocampal-cortical representations corresponding to multiple-to-one associations reflect the ability of neural connection in abstracting similar and repeated features of ongoing tasks.

Researches show that hippocampal-cortical communications connect specific-to-general links (90, 103). In a mouse study of reversal learning problems with same structure but different physical implementations, the PFC showed similar representations across problems, suggesting its role in abstracting common structure for generalization, while hippocampus is more highly influenced by specific problems, indicating it takes charge of the specific structure of the current situation (170). In addition, Zhou *et al.* reported that hippocampus and the OFC of rodents function complementarily in familiar environments, that the OFC encode current situation while hippocampus ensembles support prospective memory for future performance in a cognitive map (171). Through concept-learning tasks in humans with model-based fMRI, Bowman *et al.* found that anterior hippocampus and the vmPFC work together to modulate the abstraction of concept during generalization via abstracting information integrated from multiple events, particularly, hippocampus integrates and forms generalized memory representations, while the vmPFC contributes by representing these abstract categories and aiding their applications to new situations (172). In human-related study, Mizrak *et al.* demonstrated through fMRI studies that hippocampus and OFC highly correlated to differentiate between context-determined and context invariant task structures after learning, suggesting their cooperation in guiding selections of future decision strategies (173). Though there are few studies displaying the hippocampal-cortical neural connections for common structure/role abstraction in different tasks, which are the basis for cognitive generalization, thus further studies revealing the neural networks among hippocampus and cortex that influences cognitive generalization should be considered.

Discussion and Prospect

The ability of generalization, which reflects the ability of learning and memory, is crucially required for adaption of novel circumstances both

animals and humans. In this study, we mainly focus on reviewing the neural mechanism on the generalization from hippocampus and cortex in rodents, primates, and humans. We summarized that hippocampus show characteristics of remapping and replay activities, which represents changed states in new but similar task contexts applied to abstract rules. The activation of PFC, PPC, and OFC is necessary for decision-making and goal achievement through context dependent abstract rules. Single neural activity and neural geometry both display heterogeneity and generality of PFC when abstract rules are formed and used for guiding behaviors to assessment of decisions. PPC, by virtue of its vast connectivity, participates in multiple cognitive processes, especially in decision-making, planning and categorization. It also mediates some abstract and symbolic cognitive capacities. PPC neurons represent previous sensory experience to guide decision-making on new sensory stimuli. OFC is a key brain region in reward evaluation. Its feature of updating value judgments supports abstract representation of decision-making. All these studies through rodents, primates, and humans have implicated the potential neural mechanisms of generalization, laying a solid foundation for understanding the neural basis of cognitive function.

Remapping, a hallmark of cognitive flexibility, occurs when encountering a new situation, based on the fact that the new situations share similar feature with previous experiences. However, it is counterintuitive that remapping may indicate generalization. Because remapping means variations in different forms of neural activities to deal with changes of sensory or cognitive inputs, while generalization suggests that neurons show common activity patterns to respond similar but slightly different environments or perceptual inputs. Interestingly, it was shown that single neurons in primate hippocampus exhibit similar functions as rodent's place cells to encode space information through value place fields, which can be remapped to adapt changed but gradually correlated environments, leading to generalization of maps (72). This contradiction could be explained due to different reference coordinate system. The positional changes of external sensory inputs result in neural remapping, while when treating sensory inputs as reference coordinate system, the similar neural patterns occur in response to different environments. Taking an example of goal-vector cells, which are active at certain distances and directions from goals to permit rapid generalization to novel goals in novel environments (72, 174), based on the fact that the new situations share similar feature with previous experiences. Therefore, we may propose a hypothesis that neuronal ensembles carrying generalization properties could remap in a direction-guided manner according to changes in different environments.

Hippocampal neurons change dynamically to realize cognitive generalization. Most studies focused on the populational ensembles of place cells and their functional connection of remapping and replay with cognitive generalization. However, hippocampal place cells are only accounted for half of the recorded population. It was recently reported that, there is a distinct subset of neurons in hippocampal CA1 exhibits weak spatial selectivity but gradually develops correlated activity with place cells, thus effectively links discrete place fields of place cells into map-like structure after latent learning and during sleep (175). Through large-scale longitudinal two-photo calcium imaging of hippocampal CA1 neurons, it was found that hippocampal neural activity progressed along with improved animal behavioral efficiency and showed similar patterns within and across tasks, but undergoes a series of decorrelation steps and finally resulted in orthogonalized task-specific representations, indicating the dynamic changes of hippocampal population plays crucial role in generalizing learned states into novel situations (176). Contrasted to the place cells with consistent and temporally adjacent spiking in spatial place fields, isolated spikes in hippocampal CA1 were found to preferentially occurs during hippocampal theta oscillations and transiently encodes nonlocal spatial situation, indicating its association with the evaluation of distant physical locations. Furthermore, these events are coordinated with ongoing activity of PFC, evidencing the interactions across brain regions, especially hippocampal-prefrontal cortical networks (177). These studies suggest the heterogeneity of hippocampal neurons and their coordination with multiple brain networks should be considered for their possible neural representations in cognitive generalization.



In this manuscript, we reviewed different brain regions of cortex, especially the PFC, OFC, and PPC, in cognitive generalization across different species. It is known that PFC functions as a critical hub in the brain to manipulate many high ordered cognitive behaviors, such as future planning, problem solving, new environments adapting, and so on. Due to ethical issue, many related studies are based on single neuron recordings or neural circuit regulation in nonhuman (rodents and primates) models. However, the connectivity patterns, parcellation, and layered structure of PFC in humans are different from rodents, but to a lesser extent in primates (178). In anatomical view, rodents have a putative homolog of the agranular medial frontal cortex and OFC of primates; while, the granular frontal cortex (dlPFC) lacking in rodents is composed of the largest part of PFC in most primate species (179, 180). Evolutionally, basal primates possess a small granular PFC, while more advanced simian species, like humans own an increasingly larger granular PFC (178, 181). In functional view, the PFC across species exhibits a high degree of functional homology, particularly when considering its involvement in complex cognitive functions like decision-making, memory, and abstract rule learning (178). For instance, the mPFC in rodents mediates similar cognitive functions like decision-making and attention as that in primates and dlPFC in humans, although they are not anatomically equivalent (182). OFC is phylogenetically originated from PFC in humans, that has essential role in value-based decision-making. Ongur and Price have demonstrated that the laminar organization and cellular distribution in the OFC of humans and monkeys share similar features (183). Comparative neuroanatomical studies also made clear that, central OFC and vmPFC in monkeys are homologous to that in humans separately and belong to distinct networks (184). Lesions with OFC in different species all exhibited similar features that impairments occurs in reversed contingencies, but not in learning (111, 185–187), suggesting the OFC composes a common framework for processing generalization across species. However, when issuing these cortical regions in cognitive-related functions, there are still discrepancies existing since there are differences in multiple aspects, including anatomical differences across species, different behavioral tasks applied as well as different neural recording methodologies for evaluation of the connectivity between neural activity and behaviors. Therefore, future research should bridge methodological and task-based differences to explore the role of hippocampal-cortical networks in cognitive generalization across different species.

Cognitive generalization requires concept/rule/structure abstraction and the formation of higher-order representations. This process necessitates capturing precise neural dynamic to represent abstract rules, concepts and decision-making, as well as measuring large-scale network activity to unveil functional connections among brain regions, including hippocampus, and PFC and associative cortical areas. As evidenced in many studies, single-unit or populational (LFP) recordings are basically applied in studies of rodents/primates, which exhibit high spatial and temporal resolutions and provide direct insight into how individual neurons encode specific roles versus specific experiences, or how neural populations represent hippocampal replay to link memory retrieval to memory generalization. But it only limited its use in animals or neurosurgical patients and also fail to displaying broader network interactions. For human studies, fMRI is a powerful tool that owns high spatial resolution for identifying localization of brain regions (e.g., vmPFC, hippocampus) involved in rule abstraction and can also track cross-brain network interactions in generalization. However, fMRI has poor temporal resolution and only measures indirect neural activity. Therefore, a multimodal, integrative approach combining high temporal and spatial resolution techniques will provide the most comprehensive insights into how the brain generalizes knowledge across different contexts.

Studies have shown impairment of cognitive generalization is tightly related to neurological diseases. In preclinical, autosomal dominant AD mutation carriers exhibit significant memory generalization impairment, which is associated with the left hippocampal volume (188). In a recognition and categorization of visual dot pattern tasks, impaired ability of recognition was shown in patients with both mild AD and moderate AD and impaired categorization found in patients with moderate AD (189). In a study of AD, it was reported that the remapping activity of hippocam-

pal CA1 neurons is severely disrupted and the grid cells in MEC impaired in model mice of AD, indicating that memory generalization deficits in AD might be associated with hippocampal remapping dysfunction and disrupted hippocampal-MEC circuits (190), which could be further studied. In addition, dysfunction of the mPFC has been found in various neurological and psychiatric disorders, such as depression, anxiety disorders, schizophrenia, autism spectrum disorders (ASD) (191). Patients with schizophrenia display deficits in abstracting perceptual categorization and are strongly drawn attention from task-irrelevant conflicting abstract rules (192). Their memory deficits are associated with hypoactivation in caudal LPFC regions and hyperactivation in rostral LPFC regions (193). Young kids with ASD have difficulties of learning abstract rules, while adults with ASD struggle to categorize atypical exemplars and form prototypical presentation (194, 195). These neurological diseases further reflect the functional integrity of PFC is necessary for generalization. This will further provide clues (which might be potential biomarkers or preclinical diagnosis) for generalization dysfunction-related neurological diseases and shed light on the intervention and treatment of these diseases.

Acknowledgments

We thank the support from Biological and Medical Engineering Core Facilities of Beijing Institute of Technology.

Author Contributions

Z.Q. and H.Q. conducted and designed the studies; Z.Q. and D.S. wrote the manuscript and D.S. plotted the figures. The manuscript has been read and approved by all authors. All authors take full responsibility for all figures and text and approve the content and submission of the study. No related work is under consideration elsewhere.

Corresponding authors: Professor Z.Q. for any aspect of the work except for figures and Professor H.Q. for whole manuscript. These corresponding authors take full responsibility for the submission process.

Funding Sources

This work was supported by the Ministry of Science and Technology Key project (grant no. 2022ZD0206800) and the National Natural Science Foundation of China (grant no. 82371441, 82371446), Beijing Nova Program (grant no. 20220484083; 20230484436) and Beijing Municipal Natural Science Foundation (grant no. IS23093; 7222113).

Competing Interests

The authors have confirmed that no conflict of interest exists.

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